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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Hubert METZNER et al.	Group Art Unit: 1654
Application No.: 09/809,021	Examiner: Michael V. Meller
Filed: March 16, 2001	
For: THROMBIN PREPARATIONS AND PROCESS FOR THEIR PRODUCTION	Confirmation No.: 5147

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed May 9, 2007, and further to Board Rule 41.37, Appellants present this brief and enclose herewith a check for the fee of $500.00 required under 37 C.F.R. § 1.17(c). This Appeal responds to the final rejection of claims 49-61 mailed January 10, 2007.

This Appeal Brief is being filed concurrently with a petition for a **One-Month Extension of Time** until today, August 9, 2007, and a further sum of $120.00 to cover the extension of time charges. If any additional fees are required or if the enclosed payment is insufficient, Appellants request that the additional, required fees be charged to Deposit Account No. 06-0916.

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Real Party In Interest

CSL Behring GmbH is the real party in interest. CSL Behring GmbH is formerly known as ZLB Behring GmbH, which, in turn, is formerly known as Aventis Behring GmbH. The assignment to Aventis Behring GmbH was recorded on September 16, 2001, at Reel 011624, Frame 0455. The change of name to ZLB Behring GmbH was recorded at Reel 015366, Frame 0733, on November 10, 2004. The change of name to CSL Behring GmbH will be filed with the Office shortly.

Related Appeals and Interferences

In accordance with 37 C.F.R. § 41.37(c)(1)(ii), Appellants advise the Board of Patent Appeals and Interferences that the present application was the subject of earlier Appeal No. 2005-0192. A copy of the Board's decision is attached.

The Appellants, undersigned, and Assignee are not aware of any other appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

Status of the Claims

Claims 20-24, 27-30, 33, and 49-61 are presently pending, as original claims 1-17, as well as claims 18-19, 25-26, 31-32, and 34-48 have been canceled in earlier prosecution.

Of the presently pending claims, claims 49-61 are finally rejected and are the subject of this Appeal.

Claims 20-24, 27-30, and 33 have been withdrawn from consideration by the Examiner. However, those withdrawn claims depend from elected claim 49 and are

drawn to methods of making and using the composition of claim 49. Hence, those claims may be re-joined to elected claims 49-61 according to the policy of M.P.E.P. § 821.04.

The actual list of claims on appeal and their present status is provided in the Appendix.

Status of Amendments

All prior Amendments have been entered by the Examiner.

Summary Of Claimed Subject Matter

The instant invention, as recited in independent claim 49, is a stable thrombin preparation that comprises thrombin protein and a noncovalently binding inhibitor of thrombin activity as stabilizer. The composition also comprises at least one soluble calcium salt, sodium chloride as stabilizer, at least one buffer substance, and at least one of: a sugar, a sugar alcohol, an amino acid, a salt of a mono- or polycarboxylic acid, or a salt of a mono-or polyhydroxycarboxylic acid. Furthermore, the stable thrombin preparation has the following properties. The preparation, after at least 12 months of storage at 20-25 °C in the liquid state, maintains a thrombin activity that is more than 70% of its initial level prior to the storage. That thrombin activity is measured with a coagulation test with a fibrinogen substrate.

This claim is supported by the application as a whole. Particular support may be found, for example, in original claims 1 and 2, reciting the ingredients listed in claim 49. (See the Specification at page 16.) Claim 49 is further supported at the first full paragraph on page 3, the second full paragraph on page 6, and at the paragraph bridging pages 6 and 7, describing the stability of the preparations upon storage. Further, Example 5, Tables 4 and 5 at pages 12 and 15 present data showing that two thrombin preparations according to the claim (numbers 8 and 9) retain about 80-90% of their original thrombin activity after 12 months of storage at 20-25 °C, according to a coagulation test with a fibrinogen substrate, while other preparations retain only about 40-65% of the original thrombin activity under these conditions.

Claim 50 depends from claim 49 and recites that the thrombin activity after at least 12 months of storage at 20-25 °C in the liquid state is more than 80% of its initial level prior to the storage. This claim is also supported by the application as a whole, including the above locations, such as the first full paragraph on page 3, the second full paragraph on page 6, and at the paragraph bridging pages 6 and 7, describing the stability of the preparations upon storage, and the data for preparations 8 and 9 shown in Tables 4 and 5. Those data show that those preparations retain about 80-90% of their original thrombin activity after 12 months of storage at 20-25 °C, while other preparations retain only about 40-65% of the original thrombin activity under these conditions.

Claim 51 depends from claim 49 and recites that the thrombin activity after at least 12 months of storage at 20-25 °C in the liquid state is more than 90% of its initial level prior to the storage. Particular support for this claim may be found, for example, in Tables 4-5 in which the thrombin activity values of two exemplary preparations according to the invention, preparations 8 and 9, after storage at the claimed temperature range, are 100.9% and 90.6% after 12 months.

Claim 52 depends from claim 49 and recites that the thrombin activity after at least 24 months of storage at 20-25 °C in the liquid state is more than 70% of its initial level prior to the storage. This claim is also supported by the application as a whole, particularly at Tables 4-5 at pages 12 and 15 of the application. Those tables show that two preparations according to the claims (preparations 8 and 9) retain 90.1% and 82.4% of their original thrombin activity after 24 months of storage at the claimed temperature range. Claim 52 is further supported at the first full paragraph on page 3, the second

full paragraph on page 6, and at the paragraph bridging pages 6 and 7, describing the percent thrombin activity of claimed preparations upon storage.

Claim 53 depends from claim 49 and recites that the thrombin activity after at least 24 months of storage at 20-25 °C in the liquid state is more than 80% of its initial level prior to the storage. This claim is supported as for claim 52 discussed above.

Claim 54 depends from claim 49 and recites that the thrombin activity after at least 12 months of storage at 20-25 °C in the liquid state is more than 90% of its initial level prior to the storage. Support for this claim, may be found in Tables 4-5, in which preparation 8 retains 90.1% of its original thrombin activity after 24 months of storage.

Claims 55 and 56 depend from claim 49 and recite that the noncovalently binding inhibitor of thrombin activity is benzamidine or p-aminobenzamidine, respectively. These claims are supported, for example, at the first full paragraph of page 6 and the paragraph bridging pages 6 and 7, and in original claim 10.

Claim 57 depends from claim 49 and recites that the pH of the preparation is from 5.0 to 8.0. This claim is supported, for example, at the paragraph bridging pages 5 and 6, and in original claim 7.

Claim 58 depends from claim 49 and recites that the preparation comprises a sugar alcohol at a maximum concentration of 2% (w/v). This claim is supported, for instance, at Table 4, at page 12, describing preparations containing 0 %, 1 %, and 2 % mannitol. It is further supported at page 3, lines 11-14, for example.

Claim 59 depends from claim 49 and recites that the at least one of a sugar, a sugar alcohol, an amino acid, a salt of a mono- or polycarboxylic acid, or a salt of a

mono-or polyhydroxycarboxylic acid does not increase the viscosity of the preparation. This claim is particularly supported at page 3, lines 11-14, for example.

Claims 60 and 61 depend from claim 49 and recite that the preparation comprises a hemostatic or a constituent of a hemostatic (claim 60) or a constituent of a tissue glue (claim 61). These claims are supported, for instance, by original claims 15-17, as well as at page 1, second full paragraph.

Because withdrawn claims 20-24, 27-30, and 33 are not part of the instant appeal, they are not discussed in detail in this section. They are nonetheless provided in the Appendix. These claims recite methods of making and using the thrombin preparations of claim 49.

Finally, please also note that the present claims do not include means plus function or step plus function limitations according to 35 U.S.C. § 112, sixth paragraph.

Grounds of Rejection

A. Claims 49-61 stand finally rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking enablement for the full scope of the claims.

B. Claims 49-61 stand finally rejected under 35 U.S.C. § 112, First Paragraph, as allegedly lacking written description support.

C. Claims 49-61 stand finally rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Lorne or Allary in view of Hanada, Brezniak, and Altshuler. (Lorne et al. *Rev. Fr. Transfus. Hemobiol.* 32: 391-400 (1989) (a complete translation was made of record by the Examiner); Allary et al. *Ann. Pharmaceutiques Francaises* 48: 129-35 (1990) (a complete translation was made of record by the Examiner); Hanada et al., U.S. Patent No. 5,945,103; Brezniak et al., *Blood Coag. and Fibrinolys.* 5: 847-8 (1994); and Altshuler, U.S. Patent No. 4,363,319.)

D. Claims 49-61 stand finally rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Tripier in view of Lorne or Allary, and further in view of Hanada, Brezniak, and Altshuler. (Tripier et al., U.S. Patent No. 5,322,926.)

For the purposes of each of those rejections, claims 49-61 stand or fall separately, with the exception that claims 55-57 and 59-61 are grouped together with claim 49 for purposes of the written description requirement discussed in Section B below.

Argument

A. Rejection of Claims 49-61 Under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner first rejects all of claims 49-61 as allegedly lacking enablement. (Office Action at pages 2-5.) Appellants address that rejection with respect to all claims separately below.

Before proceeding to discuss the rejection with respect to each claim, however, Appellants note that essentially the same rejection has already been raised and overcome in prior prosecution. Specifically, Appellants' prior Appeal Brief of May 19, 2004, addressed an analogous rejection over the then pending claims, and was subsequently withdrawn in the Examiner's Answer of July 29, 2004.

Moreover, as explained below, the rejection as applied to all of the claims is not a *prima facie* case of enablement because the Examiner has focused on predictability without considering other enablement factors discussed at M.P.E.P. § 2164.01(a) and *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), and because the Examiner supports his conclusions with conclusory statements rather than with fact-based reasoning according to the substantial evidence standard of *In re Zurko,* 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001).

1. Claim 49

In this enablement rejection, the Examiner applies far too stringent a standard and supports the assertion of non-enablement by only general, conclusory statements, such as "biotechnology is a highly unpredictable art" rather than with substantive

evidence based on factual, scientific reasoning. (See the Office Action at page 3, second complete paragraph, for example.)

Moreover, predictability or lack thereof is not the test by which enablement is judged. Instead, the test of enablement is whether the experimentation needed to practice the invention as claimed is "undue." M.P.E.P. § 2164. Determining whether or not experimentation is "undue" involves many factors, of which the level of predictability is only one. M.P.E.P. § 2164.01(a); *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Those other factors, described in *In re Wands*, at 737-8, and listed at M.P.E.P. § 2164.01(a), include the nature of the invention, the state of the prior art, the level of guidance provided by the application and prior art.

The present invention is a stable thrombin preparation which may be prepared by mixing ingredients. The thrombin activity after storage of such preparations can be assayed by storing the solutions for the requisite period of time at the recited temperature range, then testing the remaining thrombin activity using a routine coagulation test with a fibrinogen substrate, as described in the application's working example 5. Furthermore, exemplary preparations falling inside and outside the scope of the instant claim 49 are provided in Tables 4 and 5 at pages 12 and 15 of the application to help guide one of ordinary skill. (*See, e.g.*, preparations 8 and 9, which fall within the claimed parameters of having thrombin activity at least 70% of its original level after 12 months of storage at the claimed temperature.)

Thus, all of the procedures needed to make the claimed preparations and to test the thrombin activity after storage are routine to one of ordinary skill in the art and are well guided by the application. Even assuming the stability of formulations claimed in

claim 49 is highly unpredictable as the Examiner contends, the Federal Circuit in *Wands* particularly pointed out that an unpredictable invention may be enabled despite requiring "a considerable amount of experimentation . . ., if [the experimentation] is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 858 F.2d at 737 (citations omitted). In other words, the level of predictability must be balanced against the other factors including the level of ordinary skill in the art and the amount of guidance provided in the application and the prior art as to how to make and use the invention.

In addition, generic claims in an unpredictable art are allowed to encompass a certain number of inoperative embodiments. *In re Angstadt*, 537 F.2d 489 (C.C.P.A. 1976). For example, *In re Angstadt* involved a claim generically reciting a "catalyst." The issue in the case was whether the generic claim reciting a "catalyst" was enabled, or whether only the specific catalysts used in the patent's text were enabled. As the court explained, "[t]he question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by the claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts . . . such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed." 190 U.S.P.Q. at 218 (footnote omitted). In *Angstadt*, as here, the patent's disclosure was sufficient to point

an experimenter toward appropriate ingredients falling within the generically claimed class.

Thus, the Examiner has not made a *prima facie* case of enablement against claim 49 and Appellants request the Board to overturn this rejection.

2. Claim 50

The Examiner makes the same enablement rejection to claim 50 and Appellants also request this rejection to be overturned. The difference between claim 49 and claim 50 is a requirement for thrombin to retain more than 80% rather than more than 70% of its original activity after the claimed storage. Tables 4 and 5 at pages 12 and 15 of the application show exemplary preparations that retain such stability contrasted with others that fall outside the scope of the claims. (Compare preparations 8 and 9 to preparations 1-7 and 10-12.) Moreover, preparing and testing the thrombin activity of the compositions involves routine procedures such as mixing ingredients and carrying out a standard thrombin activity test known to those in the art.

The routine nature of those procedures and the guidance provided by the application of preparations falling inside and outside of the scope of claim 50 demonstrates that claim 50 is also enabled. Indeed, even assuming the invention of claim 50 is highly unpredictable as the Examiner suggests, the Federal Circuit in *Wands* specifically pointed out that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 858 F.2d at 737 (citations omitted).

3. Claim 51

Appellants also request this rejection to be overturned with respect to claim 51. The difference between claim 49 and claim 51 is a requirement for thrombin to retain more than 90% rather than more than 70% of its original activity after the claimed storage. The claimed preparations 8 and 9 in Tables 4 and 5 retain such stability. (Specification at pages 12 and 15.) As stated above, preparing and testing the thrombin activity of the compositions moreover involves routine procedures, which weigh against the Examiner's concern as to the level of predictability.

4. Claim 52

Appellants also request this rejection to be overturned with respect to claim 52. The difference between claim 49 and claim 52 is a requirement for thrombin to retain more than 70% of its original activity after a longer storage time of at least 24 months rather than at least 12 months. Tables 4 and 5 show exemplary preparations that retain such stability. (Specification at pages 12 and 15, preparations 8 and 9.) Again, preparing and testing the thrombin activity of the compositions moreover involves routine procedures and is well guided by the application. Those factors counterbalance the alleged lack of predictability raised by the Examiner.

5. Claim 53

The difference between claim 49 and claim 53 is a requirement for thrombin to retain more than 80% of its original activity after a storage time of at least 24 months rather than more than 70% of its original activity after a storage time at least 12 months. Preparations 8 and 9 of Tables 4 and 5 also meet that requirement. (Specification at pages 12 and 15.) Again, preparing and testing the thrombin activity of the

compositions moreover involves routine procedures and is well guided by the application.

6. Claim 54

The difference between claim 49 and claim 54 is a requirement for thrombin to retain more than 90% of its original activity after a storage time of at least 24 months rather than more than 70% of its original activity after a storage time at least 12 months. Preparation 8 of Tables 4 and 5 meets that requirement. (Specification at pages 12 and 15.) Once again, preparing and testing the thrombin activity of the compositions moreover involves routine procedures.

7. Claim 55

The difference between claim 49 and claim 55 is a requirement for benzamidine as the noncovalently binding inhibitor of thrombin activity. Preparation 9 of Tables 4 and 5 meets that requirement. (Specification at pages 12 and 15.) Once again, preparing and testing the thrombin activity of the compositions moreover involves routine procedures.

8. Claim 56

The difference between claim 49 and claim 55 is a requirement for p-aminobenzamidine as the noncovalently binding inhibitor of thrombin activity. Preparation 8 of Tables 4 and 5 meets that requirement. (Specification at pages 12 and 15.) Once again, preparing and testing the thrombin activity of the compositions moreover involves routine procedures.

9. Claim 57

The difference between claim 57 and claim 49 is a requirement for a particular pH range for the preparation in claim 57. The pH can be tested by routine procedures such as a pH meter prior to, during, and after storage, to determine whether it falls within the claimed range of 5.0 to 8.0. Preparations 8 and 9 depicted at pages 12 and 15 of the application have an initial pH of 6.0, thus falling within the claimed range.

10. Claim 58

Claim 58 differs from claim 49 by an additional requirement that the preparation comprises a sugar alcohol at a maximum concentration of 2% (w/v). As shown in tables 4 and 5, preparations 8 and 9 both meet the requirements of claim 58. (Specification at pages 12 and 15.) Those reduced to practice examples guide one of ordinary skill that preparations meeting the claimed stability requirements may be prepared with a low volume of sugar alcohol.

11. Claim 59

Claim 59 differs from claim 49 by an additional requirement that addition of the sugar, sugar alcohol, amino acid, salt of a mono- or polycarboxylic acid, or salt of a mono- or polyhydroxycarboxylic acid, does not increase the viscosity of the solution. The viscosity of the solution before and after such addition may be tested by routine procedures such as turbidimetry. Furthermore, preparations 8 and 9 depicted in Tables 4-5 at pages 12 and 15 of the application demonstrate that the claimed stability parameters may be met with low volumes of a viscous ingredient such as a sugar alcohol.

12. Claim 60

Claim 60 adds the requirement to claim 49 that the preparation comprises a hemostatic or a constituent of a hemostatic. The arguments above for claim 49 apply equally to claim 60. Hence, Appellants refer the Board to that section.

13. Claim 61

Claim 61 adds the requirement to claim 49 that the preparation comprises a hemostatic or a constituent of a hemostatic. The arguments above for claim 49 apply equally to claim 61. Hence, Appellants refer the Board to that section.

In summary, the Examiner has not raised a prima facie case of lack of enablement against any of claims 49-61, as the Examiner has not considered all of the *Wands* factors and has supported the rejection with merely conclusory statements that do not meet the substantial evidence standard of *Zurko*. Furthermore, as demonstrated by the guidance and worked examples of the application as a whole, Appellants claims 49-61 are each enabled throughout their full scope, and Appellants request the Board to overturn the enablement rejection to each of those claims.

B. Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Appellants also request the Board to overturn the Examiner's written description rejection to each of claims 49-61. (See the Office Action at pages 5-6.) The claims are discussed separately below with the exception of claims 55-57 and 59-61, which are addressed together and may stand or fall with claim 49 for purposes of this written description rejection.

The basis of the Examiner's rejection of all of claims 49-61 is that the application, in his opinion, does not support the claimed recitations of particular percentages of thrombin activity after storage for the specified time periods recited in claims 49-54 and that the application does not support the recitation of claim 58 for a sugar alcohol concentration of no more than 2% (w/v). Claims 55-57 and 59-61 are presumably included in the Examiner's rejection because they depend from rejected claim 49.

Before addressing each claim separately, however, Appellants note that written description support does not require literal, word-for-word, recitation in the descriptive text. M.P.E.P. § 2163. Instead, the specification may also implicitly or inherently support the claims, such as through the figures, the data in the working examples, and in the more general statements of the text. M.P.E.P. § 2163 and § 2163.02. For instance, in *Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC,* 72 U.S.P.Q.2d 1190, 1199 (Fed. Cir. 2004), a claim element reciting that the thickness of one part of a structure was wider than another part of the structure was sufficiently supported in the application because the relative widths in question could be seen from one of the figures, even though the relative widths were not described in words.

1. Claim 49

The Examiner contends that the application lacks written description support for the recitation in claim 49 that the thrombin preparation retains more than 70% of original thrombin activity after at least 12 months in storage at the claimed temperature range. However, as Appellants have previously pointed out, those claim limitations are nearly literally supported at page 3, lines 8-9, and page 6, entire page. For example, page 3, lines 8-9, of the application states that prior art processes did not allow for preparations

"whose thrombin activity after 12 months of more is still over 70-80% of the initial level, to be produced." Page 6, second full paragraph, goes on to explain: "It is possible via the process of the invention to produce thrombin preparations which can be stored in the liquid and/or frozen state for months or years and whose activity does not fall below 70-80% in this period." Claim 49 is also supported by actual reduction to practice of two species, preparations 8 and 9 shown in Tables 4 and 5, at pages 12 and 15. Those preparations retain 100.9% and 90.6% thrombin activity at 12 months of storage at 20-25 °C as illustrated in Table 5 at page 15.

For all of those reasons, the preparation of claim 49 squarely falls within the recited thrombin activity parameters. Hence, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 49 at the relevant date, and Appellants request the Board to overturn this rejection.

In addition, the Examiner's reasoning for rejecting claim 49, with all due respect, does not appear logically coherent to Appellants. Thus, it does not support a *prima facie* case of lack of written description. The Examiner first acknowledges that "[t]he specification states that the thrombin activity is over 70-80% of the initial level." (Office Action at page 5, second full paragraph.) But then the Examiner concludes that somehow an activity that is "over 70-80% of the initial level" is not the same thing as an activity that is "more than 70-80%" of the initial level" even though those two phrases are synonymous in the English language. (*Id.*) Appellants simply do not understand how the Examiner can conclude that "over 70-80%" means something different than "more than 70-80%," particularly as Table 5 provides examples which illustrate how to interpret the statements in the application. For example, in Table 5, the initial level of

thrombin activity is set to 100% (Table 5, top line of table, at page 15 of the application) and the activity remaining after storage is compared to that initial level (Table 5, line at 12 months storage). In preparations 8 and 9, the remaining activity is about 90-100%, clearly more than the claimed 70%. (See the Specification at page 15.)

2. Claim 50

The Examiner contends that the application does not support the limitation of claim 50 that the thrombin activity remains at more than 80% of its original level after at least 12 months at the recited temperature range. The Examiner applies the same reasoning to claim 50 as to claim 49. (See Section 1 above.) As described above with respect to claim 49, that reasoning does not appear to be logically coherent to Appellants, and hence, is insufficient to support a *prima facie* case.

As with the limitations of claim 49, the thrombin activity limitations of claim 50 are supported at several places in the application. The specification at page 3, lines 8-9, and page 6, entire page, provides near literal support for the stability requirement of claim 50. For example, page 3, lines 8-9, of the application states that prior art processes did not allow for preparations "whose thrombin activity after 12 months of more is still over 70-80% of the initial level, to be produced." Page 6, second full paragraph, goes on to explain: "It is possible via the process of the invention to produce thrombin preparations which can be stored in the liquid and/or frozen state for months or years and whose activity does not fall below 70-80% in this period." Table 5, samples 8 and 9, demonstrate actual reduction to practice of species falling within the scope of claim 50. (See the Specification at pages 12 and 15.) Those preparations

retain about 90% and 100% of the initial level of thrombin activity after the claimed storage period. Hence, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 50 at the relevant date.

3. Claim 51

The Examiner also contends that the limitation of claim 51 that the preparation retains more than 90% of its original thrombin activity after a period of at least 12 months at 20-25 °C is unsupported in the application. The Examiner's reasoning for rejecting this claim is to state merely that "support that applicant claims is in the specification is not there" without further explanation. (Office Action at page 5.) Such a conclusory statement does not support a *prima facie* case of lack of support. Moreover, the Examiner does not appear to have addressed Appellants' earlier comments about where the support is to be found. (*See, e.g.*, the Reply to Office Action filed November 2, 2006, at pages 13-14.)

However, such results are actually demonstrated in Tables 4 and 5 at pages 12 and 15. Samples 8 and 9 retain 100.9% and 90.6% thrombin activity at 12 months of storage at 20-25 °C, respectively. Given that this table demonstrates actual reduction to practice, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 51 at the relevant date, and Appellants request the Board to overturn this rejection.

Applicants further note that specific numerical ranges such as "more than 90%" may also be inherently supported by data in an application. M.P.E.P. § 2163 and § 2163.02. Table 5, for instance, presents particular examples of the claimed

preparations that retain 90.1% or 90.6% or 100.9% of their original stability after the claimed time period and at the claimed temperature range. Given measurement errors inherent in scientific calculations, one of ordinary skill in the art would recognize that a percentage of 90.1% could alternatively be reported as a percentage of 90% and a percentage of 90.6% could be reported as a percentage of 91% if fewer significant figures are used in reporting the results. For those reasons, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 51 at the relevant time.

Moreover, numerical ranges, like other claim elements, do not need to be supported by literal recitation. For example, in the case of *In re Wertheim*, working examples showing 35% and 50% of a particular ingredient within a claimed composition, coupled with a written statement about a range of 25% to 60%, was found sufficient to support a claimed range of 36% to 60%. 191 U.S.P.Q. 90, 93-97 (C.C.P.A. 1976). In other words, disclosure of a value of 35% sufficiently approximated the claimed end point of 36%.

4. Claim 52

The Examiner contends that the application lacks written description support for the recitation in claim 52 that the thrombin preparation retains more than 70% of original thrombin activity after at least 24 months in storage at the claimed temperature range. The Examiner's reasoning for rejecting this claim is as for claim 49, discussed in Section 1 above. As stated in Section 1, that reasoning does not support a *prima facie* case.

Moreover, the limitations of claim 52 are supported at several places in the application, such as in Table 5 at page 15 of the application, where such results are actually reduced to practice. (See samples 8 and 9, which retain 90.1% and 82.4% thrombin activity at 24 months of storage at 20-25 °C.) Page 3, lines 8-9, of the application also states that prior art processes did not allow for preparations "whose thrombin activity after 12 months of more is still over 70-80% of the initial level, to be produced." Page 6, second full paragraph, goes on to explain: "It is possible via the process of the invention to produce thrombin preparations which can be stored in the liquid and/or frozen state for months or years and whose activity does not fall below 70-80% in this period."

Hence, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 52 at the relevant date.

5. Claim 53

The Examiner contends that the application does not support the limitation of claim 53 that the thrombin activity remains at more than 80% of its original level after at least 24 months at the recited temperature range. Again, the Examiner's reasoning for rejecting claim 53 is the same as that discussed above with respect to claim 49 in Section 1. That reasoning does not rise to the level of a *prima facie* case.

In addition, the limitations of claim 53 are supported at several places in the application, including in Table 5, where they are actually reduced to practice. (See the application at page 15, samples 8 and 9, which retain 90.1% and 82.4% thrombin activity at 24 months of storage at 20-25 °C.) Page 3, lines 8-9, of the application also

states that prior art processes did not allow for preparations "whose thrombin activity after 12 months of more is still over 70-80% of the initial level, to be produced." Page 6, second full paragraph, goes on to explain: "It is possible via the process of the invention to produce thrombin preparations which can be stored in the liquid and/or frozen state for months or years and whose activity does not fall below 70-80% in this period."

From the above information, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 53 at the relevant date.

6. Claim 54

The Examiner also contends that the limitation of claim 54 that the preparation retains more than 90% of its original thrombin activity after a period of at least 24 months at 20-25 °C is unsupported in the application. The Examiner's reasoning for rejecting this claim is as for the rejection of claim 51 discussed in Section 3 above. That reasoning is insufficient to support a *prima facie* case.

In any event, the invention of claim 54 is supported, for instance by the worked examples of Tables 4 and 5 at pages 12 and 15. Specifically, sample 8 retains 90.1% of the original thrombin activity after 24 months in storage at 20-25 °C. Given that this table demonstrates actual reduction to practice, one of ordinary skill would conclude that Appellants were in possession of the invention of claim 54 at the relevant date. Indeed, one of ordinary skill in the art would recognize that a percentage of 90.1% could be reported as a percentage of 90%, if fewer significant figures are used.

Applicants again note that specific numerical ranges may also be inherently supported by data in an application. (See also Section 3 above.) For example, in the case of *In re Wertheim*, working examples showing 35% and 50% of a particular ingredient within a claimed composition, coupled with a written disclosure of a range of 25% to 60%, was found sufficient to support a claimed range of 36% to 60%. M.P.E.P. § 2163.06(III); 191 U.S.P.Q. 90, 93-97 (C.C.P.A. 1976). In other words, a working example with value of 35% was sufficiently close to the claimed 36% end point of the claim as to support the claim under 35 U.S.C. § 112. Similarly here, a particular example of the claimed preparations that retains 90.1% of its original stability, or just over 90.0%, is sufficiently close to the claimed "more than 90%," when coupled with the general statements at pages 3 and 6 of the application, as to support claim 54.

7. Claim 58

The Examiner rejects claim 58 for the same reasons as claim 49 and also due to the recitation of a maximum of 2% (w/v) sugar alcohol in claim 58. (Office Action at page 6.)

The Examiner contends that the application lacks written description support for the recitation in claim 49, carried over to claim 58, that the thrombin preparation retains more than 70% of original thrombin activity after at least 12 months in storage at the claimed temperature range. That portion of the rejection is discussed above in Section 1 and Appellants' remarks apply equally here and will not be repeated.

The Examiner objects to the additional requirement in claim 58 for "sugar alcohol at a maximum of 2%" because, in the Examiner's opinion, referring to Table 4 at page

12, the application supports only mannitol at that concentration range. However, the use of mannitol in Table 4, coupled with the remaining disclosure, directs those of ordinary skill in the art that the concentration range which works for mannitol could be used with sugar alcohols generally, for example, glycerol. For example, the remaining text of the application refers to sugar alcohols as a whole and explains that sugar alcohols, which are generally viscous substances, may be used in low enough quantities in this invention so as not to change the viscosity of the preparation. (See the specification at original claims 1, 2, and 8, and at page 3, lines 11-14.)

Further, the M.P.E.P. explains that an example species supports claims to a genus so long as the behavior of other members of the genus is reasonably predictable based on that of the disclosed species. *See* M.P.E.P. § 2163.05(I)(section entitled: Addition of a Generic Claim). Here, the Office has provided no evidence to suggest that there is anything unique about mannitol and that other sugar alcohols such as glycerol would not behave similarly. Hence, Appellants request the Board to overturn this rejection.

8. Claims 55-57 and 59-61

The Examiner appears to have included claims 55-57 and 59-61 in this rejection merely because they depend from rejected independent claim 49. No other, independent grounds are given for rejecting these claims. Hence, Appellants remarks in Section 1 apply equally to the rejections of each of those claims and need not be repeated. For that reason, these claims are grouped together under one heading here.

In conclusion, Appellants request the Board to overturn all of the above written description rejections drawn to the language of claims 49-54 and 58 because the Examiner has not made a *prima facie* case of lack of written description support as to any of those claims.

C. Rejection Under 35 U.S.C. § 103(a) over Allary or Lorne in view of Hanada, Brezniak, and Altshuler

The Examiner next maintains the rejection of claims 49-61 over the combination of Allary or Lorne in view of Hanada, Brezniak, and Altshuler. (Office Action at 7-11.) Appellants also request the Board to overturn that rejection as to all of claims 49-61, and discuss the claims separately below.

Before proceeding to discuss each separate claim, Appellants note that obviousness is determined by performing the so-called Graham factual inquiries. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007). Those inquiries are:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary considerations.

(Memorandum of the U.S. Patent and Trademark Office to Technology Center Directors, May 3, 2007, at page 1.)

The Supreme Court in *KSR v. Teleflex* emphasized the importance of considering secondary considerations such as unexpected results, given that most, if not all, inventions are combinations of what was, in some sense, already known. *See*

KSR, 127 S.Ct. at 1741. Thus, elements that "work[] together in an unexpected and fruitful manner" may support a conclusion of nonobviousness. *Id.*

Moreover, the Supreme Court in *KSR* pointed out that when combining elements from several different prior art documents, it is important to identify "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, --- F.3d ---, 2007 WL 1839698, at 5 (Fed. Cir. June 28, 2007) (citing *KSR v. Teleflex*, 127 S.Ct. at 1731). Indeed, the Office's policies set forth in the Memorandum of May 3, 2007, advise Examiners that "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." (*Id.*, at page 2.) Evaluating motivation to combine documents and reasonable expectation of success can be helpful in determining if there is sufficient reason to combine prior art elements. (*Id.*)

In addition, a prior art reference may be used to support an obviousness rejection only for what it objectively teaches to those of ordinary skill. It is not correct to base obviousness rejections on inherent properties unless those properties are actually taught or suggested in the prior art itself when that art is taken as a whole. *See* M.P.E.P. § 2143.03. As the courts have long explained, obviousness must be based only on properties that are actually *known* before the application is filed. But inherent properties, by definition, are usually *unknown*. Something that is unknown cannot be obvious. *See In re Shetty*, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 757 (C.C.P.A. 1977),

citing *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966) (emphasis added).

Finally, the Examiner bears the burden to set forth such reasoning according to the substantial evidence standards set forth by the Federal Circuit. *See In re Zurko*, 258 F.3d 1379 (Fed. Cir. 2001); *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002). An Examiner cannot rely on "mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning" supporting a conclusion of obviousness. *KSR v. Teleflex*, 127 S.Ct. at 1741 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *and see Lee*, 277 F.3d at 1345.

1. Claim 49

The Examiner cites five documents in asserting that the invention of claim 49 is allegedly obvious: Allary or Lorne in view of Hanada, Brezniak, and Altshuler. Allary and Lorne are two publications by the same researchers presenting the same general data. Hence, they are considered together in these remarks.

There are several important differences between what is taught in those five articles and Appellants' claim 49. As a group, the articles show at best that the claimed ingredients were known to those who worked with thrombin. But the prior art does not provide any reason for one of ordinary skill knowing nothing of the instant invention to have combined those ingredients as expressed in claim 49.

For example, Allary and Lorne as a whole are primarily concerned with methods of purifying thrombin from crude solutions. The articles use L-arginine, arginine methylester, or benzamidine during one of the steps of the purification process to elute

thrombin protein from a chromatography column. That teaching certainly demonstrates that benzamidine, for example, was known and could be used as a reagent in certain chromatography purification procedures. But the two articles specifically point out that benzamidine should not be added to a stable thrombin preparation intended for storage. For instance, Lorne explains that "the thrombin obtained [after the purification] . . . must obligatorily be treated by a preliminary dialysis or ultrafiltration in 1M NaCl to dissociate the complex formed with the elution agent" (i.e. the benzamidine, L-arginine, or argininemethylester). (See the translation of Lorne at page 15, second full paragraph; Lorne at page 399, final full paragraph, referring to steps shown in Table 1, at page 398.) Both Allary and Lorne go on to remove the elution agents used during the purification process. Both publications therefore teach one of ordinary skill that a stable thrombin preparation should not contain elution agents such as L-arginine, argininemethylester, or benzamidine.

Similarly, Hanada also teaches a methods of purifying thrombin. It employs benzamidine or p-aminobenzamidine during an intermediate step in the process in which viruses are killed by trialkylphosphate. (Hanada at col. 4, lines 13-37, and col. 5, lines 25-50.) Like Allary and Lorne, Hanada at best shows that benzamidine was one of many ingredients known in the art. But, like Allary and Lorne, there is nothing in Hanada as a whole to suggest that a stable thrombin preparation should contain an ingredient such as benzamidine. Hanada teaches that the components of the trialkylphosphate treatment step are removed during the purification process, and does not teach using benzamidine in any other procedure. (*Id.*)

Brezniak and Altshuler do not correct the failure of Allary, Lorne, or Hanada to provide reason to prepare a stable thrombin preparation in the liquid state using a noncovalently binding inhibitor of thrombin activity. Neither document mentions such an inhibitor. Brezniak compares the effect of sodium and calcium chloride on thrombin preparations and concludes that sodium chloride is a superior stabilizer for thrombin than the calcium chloride used in claim 49. Thus, Brezniak also suggests that sodium chloride should be used rather than the claimed calcium chloride. Altshuler discusses thrombin preparations but comments that high concentrations of sugar alcohols (polyols) and polyethylene glycol (PEG) are sufficient to stabilize such preparations. (Altshuler at col. 4, lines 21-39.) That document suggests that a thrombin inhibitor would be unnecessary in a stable preparation.

Thus, as a group, the five cited documents show that various ingredients listed in claim 49 were known in the thrombin-related art, and that thrombin could be a component of numerous different kinds of solutions. But the Examiner's rejection is critically flawed as those five documents do not provide any reason why one of ordinary skill in the art should have combined the different ingredients as in claim 49. Indeed, preparing the solution of claim 49 would involve picking certain ingredients that the cited documents as a whole suggest are actually not necessary out of the myriad known possible additives, and then discarding other known ingredients that the cited art suggests are superior.

In addition, the Supreme Court in *KSR v. Teleflex* pointed out that the inferences of one of ordinary skill in the art may be considered in determining whether there is sufficient reason to combine references. Accordingly, Appellants also point out that

inhibitors of thrombin such as benzamidine or p-aminobenzamidine would likely have been considered undesirable ingredients to one of ordinary skill given that they could interfere with the activity of the thrombin in the pharmaceutical uses for which such a stable preparation is intended.

Nonetheless, even if, for the sake of argument, there were sufficient reasons to make the claimed thrombin preparation, the preparations of claim 49 demonstrate unexpectedly high stability during storage at room temperatures. Specifically, the claimed preparations retain more than 70% of their original thrombin activity after at least 12 months of storage at 20-25 °C. As explained at page 3 of the application, first full paragraph, none of the prior art processes allows for such stability. Hence, this secondary consideration demonstrates that the ingredients of claim 49, when put together as claimed achieve an unexpected and fruitful result, supporting a conclusion of nonobviousness. *See KSR v. Teleflex*, 127 S.Ct. at 1740. Indeed, the Examiner's earlier conclusory statement that the stability of a thrombin preparation generally is not predictable weighs against a conclusion of obviousness. (See Section A above.)

In summary, while the scope and content of the cited art show that various ingredients listed in claim 49 were known, the differences between the teachings of that art and the claims, as well as the secondary consideration of unexpected results demonstrates that claim 49 is nonobvious.

2. Claim 50

The remarks in Section 1 above apply equally to claim 50, and are therefore not repeated here. However, claim 50 requires an even higher stability in the preparations

than claim 49. Specifically, the claimed preparations retain more than 80% of their original thrombin activity after at least 12 months of storage at 20-25 °C. As explained at page 3 of the application, first full paragraph, none of the prior art processes allows for such stability. Hence, this unexpected result required by the preparations of claim 50 demonstrates that the preparations are not obvious.

3. Claim 51

The remarks of Sections 1 and 2 above apply equally to claim 51 and so are not repeated in this section. But claim 51 requires an even higher retention of thrombin activity after at least 12 months of storage at room temperatures than do claims 49 and 50. The preparations of claim 51 must retain more than 90% of the original thrombin activity as opposed to more than 70% or more than 80%. The Allary, Lorne, Hanada, Altshuler, and Brezniak publications and other prior art do not suggest that such results are possible, as commented at page 3, first full paragraph, of the specification. Hence, this result is unexpected and demonstrates that the preparations of claim 51 are not obvious.

4. Claim 52

The remarks of Section 1 also apply equally to claim 52, and thus need not be repeated here. But, like claims 50 and 51, claim 52 requires even greater unexpected results than does claim 49. The preparations of claim 52 retain at least 70% of the original thrombin activity after at least 24 months of storage at 20-25 °C rather than merely after at least 12 months of storage at those temperatures. As explained in the application at page 3, first full paragraph, that result is unexpected. Moreover, none of

the articles cited by the Examiner suggests that such a result is possible with a composition as claimed. Hence, this unexpected result demonstrates nonobviousness.

5. Claim 53

The remarks of Sections 1 and 2 above also apply to claim 53. Claim 53 requires that the preparations retain more than 80% of the original thrombin activity after a period of at least 24 months at room temperatures, as opposed to merely a period of at least 12 months recited in claim 50. Again, such a result is unexpected and is not taught by the five cited publications. (See the application at page 3, first full paragraph.) This unexpected result demonstrates that claim 53 is not obvious.

6. Claim 54

The remarks of Sections 1-3 above also apply to claim 54. Claim 54 requires that the preparations retain more than 90% of the original thrombin activity after a period of at least 24 months at room temperatures, as opposed to merely a period of at least 12 months recited in claim 51. Again, this result is unexpected and is not taught by the five cited publications. (See the application at page 3, first full paragraph.) This unexpected result demonstrates that claim 54 is also not obvious.

7. Claim 55

The remarks of Section 1 above apply equally to claim 55, which recites that the noncovalently binding inhibitor of thrombin activity is benzamidine. Thus, claim 55 is not obvious for the same reasons that claim 49 is not obvious.

8. Claim 56

The remarks of Section 1 above apply equally to claim 56, which recites that the noncovalently binding inhibitor of thrombin activity is p-aminobenzamidine. Thus, claim 56 is not obvious for the same reasons that claim 49 is not obvious.

9. Claim 57

The remarks of Section 1 above also apply equally to claim 57, which recites that the preparation has a pH in the range of from 5.0 to 8.0. Furthermore, the Examiner does not contend that the five cited publications direct one of ordinary skill in the art to choose such a pH range. Thus, claim 57 is not obvious for the same reasons that claim 49 is not obvious and for the additional reason that the prior art does not suggest the claimed pH range.

10. Claim 58

The remarks of Section 1 about independent claim 49 also apply to claim 58, and so are not repeated here.

In addition, claim 58 recites that the composition comprises a sugar alcohol at a maximum concentration of 2% (w/v). That limitation is in contradiction to prior art teachings about stable thrombin preparations. For instance, Altshuler points out that the sugar alcohols mannitol, sorbitol, glycerol, and their mixtures should be in a concentration of 10-50% for a thrombin preparation to be stable.[1] (See Altshuler at col. 4, lines 21-39.) When sugar alcohols were in amounts less than 10%, Altshuler

[1] Altshuler refers to those sugar alcohols as "polyols" meaning poly alcohols. One of ordinary skill in the art would have recognized that a sugar alcohol is a poly alcohol, and that the two terms are interchangeable.

explains that the thrombin preparations quickly lost their stability and thrombin activity. (Altshuler at Fig. 3; col. 5, lines 49-63; cols. 6-8, working examples III and VI compared to examples I, II, IV, V, VII, and VIII; and claim 1.) Other documents provide similar teachings. For example U.S. Patent No. 5,397,704, made of record March 15, 2001, suggests using about 10-40% glycerol by weight, preferably 20-30% by weight, to keep a thrombin preparation stable, while European Application No. 0 221 700 A2, also made of record March 15, 2001, suggests 25% glycerol. (*See* 5,397,704, at col. 2, line 61, to col. 3, line 2, and col. 5, lines 50-53; *see* EP 0 221 700 A2 at pages 3-5, Tables I-III.)

Thus, Altshuler and other documents in the general prior art teach away from the invention of claim 58 by suggesting that high concentrations of sugar alcohols are necessary for a thrombin preparation to be stable. In so doing, Altshuler also illustrates that the stability of the preparations of claim 58 is unexpected, as one of ordinary skill at the relevant time period would have expected a thrombin preparation with no sugar alcohol, or a low concentration of sugar alcohol to lose thrombin activity at room temperature relatively rapidly.

For those reasons, as well as the reasons provided in Section 1, claim 58 is not obvious.

11. Claim 59

The remarks of Sections 1 and 10 above also apply to claim 59. Claim 59 includes the limitations of claim 49 and further recites that the sugar, sugar alcohol, amino acid, salt of a mono- or polycarboxylic acid, or salt of a mono- or polyhydroxycarboxylic acid, does not increase the viscosity of the preparation.

As explained in Section 10, such preparations are contrary to the teachings of the prior art. For instance, Altshuler teaches that ingredients known to be viscous, such as sugar alcohols and polyethylene glycol (PEG) must be added to thrombin preparations or they will rapidly lose thrombin activity at room temperatures. (Altshuler at col. 3, lines 3-9; col. 4, lines 21-39; Figure 3; working examples I-VIII at cols. 6-8; and claims.) Brezniak also conducted thrombin stability studies in a PEG 6000-containing mediuim. (Brezniak at page 847, second column.)

For those reasons, as well as the reasons provided in Section 1, claim 59 is not obvious.

12. Claim 60

The remarks of Section 1 also apply to claim 60, as claim 60 depends from claim 49. In addition, claim 60 recites that the stable thrombin preparation "comprises a hemostatic or a constituent of a hemostatic." In other words, the preparation is part of a pharmaceutical formulation. Given that thrombin as a hemostatic is intended to have the highest possible therapeutic utility, it would have gone against the general understanding of one of ordinary skill in the art at the relevant time to add a thrombin activity inhibitor to such a preparation. Indeed, a noncovalently binding inhibitor of thrombin activity would logically be expected to decrease the therapeutic activity of thrombin. Hence, for that additional reason, claim 60 shows unexpected results and is not obvious.

13. Claim 61

The remarks of Sections 1 and 12 apply also to claim 61, and thus are not repeated here. Thrombin preparations as constituents of tissue glues are part of a pharmaceutical formulation. In such a formulation, addition of a thrombin activity inhibitor would logically be expected to decrease the therapeutic activity of the thrombin preparation, not to maintain it at a high level as claimed here. Hence, claim 61 is also not obvious given the unexpected and fruitful results this invention provides.

In summary therefore, Appellants request the Board to overturn this obviousness rejection with respect to each of claims 49-61.

D. Rejection under 35 U.S.C. § 103(a) over Tripier in view of Lorne or Allary, and further in view of Hanada, Brezniak, and Altshuler

The Examiner also rejects all of claims 49-61 as allegedly obvious over a combination of Tripier in view of Lorne or Allary, and further in view of Hanada, Brezniak, and Altshuler. (Office Action at pages 11-12.) Appellants also request the Board to overturn this rejection.

Before proceeding to discuss the rejection as applied to each of claims 49-61, Appellants note that Section C above provides a summary of the standards of obviousness under 35 U.S.C. § 103(a), and that Section C(1) discusses the teachings of five of the six documents in this combination.

1. Claim 49

Just as with the rejections discussed in Section C above, there are several important differences between what is taught in the six articles cited by the Examiner and Appellants' claim 49. As a group, the articles show at best that the claimed

ingredients were known to those who worked with thrombin. But the prior art does not provide any reason for one of ordinary skill knowing nothing of the instant invention to have combined those ingredients as expressed in claim 49. Moreover, the cited art does not provide any expectation that if those ingredients were combined as claimed, a thrombin preparation would result that would be stable at room temperatures for at least a year.

First of all, Tripier is concerned with a class of thrombin inhibitors called isohirudins and describes methods of making and administering the inhibitors as pharmaceuticals. It is not concerned with thrombin preparations. The substance benzamidine is used in a Tris and sodium chloride buffer to help purify an isohirudin material from an extract, as described at col. 8, line 55, to col. 9, line 21. The inhibitory activity of the isohirudins is also tested using a thrombin substrate, as described at col. 5, line 21, to col. 6, line 37. But the document as a whole relates to preparing isohuridins. Thus, Appellants fail to understand the relevance of Tripier to the instant claim 49, other than as showing that a class of thrombin inhibitor was known in the art.

As described in Section C, Allary and Lorne describe the same experiments by the same scientists, and as a whole are primarily concerned with methods of purifying thrombin from crude solutions. The articles use L-arginine, arginine methylester, or benzamidine during one of the steps of the purification process to elute thrombin protein from a chromatography column. That teaching demonstrates that benzamidine, for example, was a known compound and could be used as a reagent in certain chromatography purification procedures. But the two articles specifically point out that benzamidine should not be added to a stable thrombin preparation intended for storage.

For instance, Lorne explains that "the thrombin obtained [after the purification] . . . must obligatorily be treated by a preliminary dialysis or ultrafiltration in 1M NaCl to dissociate the complex formed with the elution agent" (i.e. the benzamidine, L-arginine, or argininemethylester). (See the translation of Lorne at page 15, second full paragraph; Lorne at page 399, final full paragraph, referring to steps shown in Table 1, at page 398.) Both Allary and Lorne go on to remove the elution agents used during the purification process. Both publications therefore teach one of ordinary skill that a stable thrombin preparation should not contain elution agents such as L-arginine, argininemethylester, or benzamidine.

Similarly, Hanada also teaches a methods of purifying thrombin. It employs benzamidine or p-aminobenzamidine during an intermediate step in the process in which viruses are killed by trialkylphosphate. (Hanada at col. 4, lines 13-37, and col. 5, lines 25-50.) Like Allary and Lorne, Hanada at best shows that benzamidine was one of many ingredients known in the art. But, like Allary and Lorne, there is nothing in Hanada as a whole to suggest that a stable thrombin preparation should contain an ingredient such as benzamidine or p-aminobenzamidine. Hanada teaches that the components of the trialkylphosphate treatment step are removed during the purification process, and does not teach using benzamidine in any other procedure. (*Id.*)

Brezniak and Altshuler do not correct the failure of Allary, Lorne, or Hanada to provide reason to prepare a stable thrombin preparation in the liquid state using a noncovalently binding inhibitor of thrombin activity. Neither document mentions such an inhibitor. Brezniak compares the effect of sodium and calcium chloride on thrombin preparations and concludes that sodium chloride is a superior stabilizer for thrombin

than the calcium chloride used in claim 49. Thus, Brezniak also suggests that sodium chloride should be used rather than the claimed calcium chloride. Altshuler discusses thrombin preparations but comments that high concentrations of sugar alcohols (polyols) and polyethylene glycol (PEG) are sufficient to stabilize such preparations. (Altshuler at col. 4, lines 21-39.) That teaching provides no reason to use a noncovalently binding inhibitor of thrombin activity if such other ingredients are sufficient.

Thus, as a group, the six cited documents show that various ingredients listed in claim 49 were known in the thrombin-related art, and that thrombin could be a component of many different kinds of solutions with myriad different ingredients. But, critically, the cited documents do not provide any reason to pick the ingredients of claim 49, discard other potential ingredients, and thus combine known ingredients the specific way that Appellants recite in claim 49.

In addition, the Supreme Court in *KSR v. Teleflex* pointed out that the inferences of one of ordinary skill in the art may be considered in determining whether there is sufficient reason to combine references. Accordingly, Appellants also point out that inhibitors of thrombin such as benzamidine or p-aminobenzamidine would likely have been considered undesirable ingredients to one of ordinary skill given that they could interfere with the activity of the thrombin in the pharmaceutical uses for which such a stable preparation is intended.

Nonetheless, even if, for the sake of argument, there were sufficient reasons to make the claimed thrombin preparations, the preparations of claim 49 demonstrate unexpectedly high stability during storage at room temperatures. Specifically, the

claimed preparations retain more than 70% of their original thrombin activity after at least 12 months of storage at 20-25 °C. As explained at page 3 of the application, first full paragraph, none of the prior art processes allows for such stability. Hence, this secondary consideration demonstrates that the ingredients of claim 49, when put together as claimed, achieve an unexpected and fruitful result, supporting a conclusion of nonobviousness. *See KSR v. Teleflex*, 127 S.Ct. at 1740. The Examiner's earlier conclusory statement that the stability of a thrombin preparation generally is not predictable also weighs against a conclusion of obviousness. (See Section A above.)

In summary, while the scope and content of the six cited publications show that various ingredients listed in claim 49 were known, the differences between the teachings of that art and the claims, as well as the secondary consideration of unexpected results demonstrates that claim 49 is nonobvious.

2. Claim 50

The remarks in Section 1 above apply equally to claim 50, and are therefore not repeated here. However, claim 50 requires an even higher stability in the preparations than claim 49. Specifically, the claimed preparations retain more than 80% of their original thrombin activity after at least 12 months of storage at 20-25 °C. As explained at page 3 of the application, first full paragraph, none of the prior art processes allows for such stability. Hence, this unexpected result required by the preparations of claim 50 demonstrates that the preparations are not obvious.

3. Claim 51

The remarks of Sections 1 and 2 above apply equally to claim 51 and so are not repeated in this section. But claim 51 requires an even higher retention of thrombin activity after at least 12 months of storage at room temperatures than do claims 49 and 50. The preparations of claim 51 must retain more than 90% of the original thrombin activity as opposed to more than 70% or more than 80%. The Tripier, Allary, Lorne, Hanada, Altshuler, and Brezniak publications and other prior art do not suggest that such results are possible, as commented at page 3, first full paragraph, of the specification. Hence, this result is unexpected and demonstrates that the preparations of claim 51 are not obvious.

4. Claim 52

The remarks of Section 1 also apply equally to claim 52, and thus need not be repeated here. But, like claims 50 and 51, claim 52 requires even greater unexpected results than does claim 49. The preparations of claim 52 retain at least 70% of the original thrombin activity after at least 24 months of storage at 20-25 °C rather than merely after at least 12 months of storage at those temperatures. As explained in the application at page 3, first full paragraph, that result is unexpected. Moreover, none of the six publications cited by the Examiner suggests that such a result is possible with a composition as claimed. Hence, this unexpected result demonstrates nonobviousness.

5. Claim 53

The remarks of Sections 1 and 2 above also apply to claim 53. Claim 53 requires that the preparations retain more than 80% of the original thrombin activity after

a period of at least 24 months at room temperatures, as opposed to merely a period of at least 12 months recited in claim 50. Again, such a result is unexpected and is not taught by the six cited publications. (See the application at page 3, first full paragraph.) This unexpected result demonstrates that claim 53 is not obvious.

6. Claim 54

The remarks of Sections 1-3 above also apply to claim 54. Claim 54 requires that the preparations retain more than 90% of the original thrombin activity after a period of at least 24 months at room temperatures, as opposed to merely a period of at least 12 months recited in claim 51. Again, this result is unexpected and is not taught by the six cited publications. (See the application at page 3, first full paragraph.) This unexpected result demonstrates that claim 54 is also not obvious.

7. Claim 55

The remarks of Section 1 above apply equally to claim 55, which recites that the noncovalently binding inhibitor of thrombin activity is benzamidine. Thus, claim 55 is not obvious for the same reasons that claim 49 is not obvious.

8. Claim 56

The remarks of Section 1 above apply equally to claim 56, which recites that the noncovalently binding inhibitor of thrombin activity is p-aminobenzamidine. Thus, claim 56 is not obvious for the same reasons that claim 49 is not obvious.

9. Claim 57

The remarks of Section 1 above also apply equally to claim 57, which recites that the preparation has a pH in the range of from 5.0 to 8.0. Furthermore, the Examiner does not contend that the five cited publications direct one of ordinary skill in the art to choose such a pH range. Thus, claim 57 is not obvious for the same reasons that claim 49 is not obvious and for the additional reason that the prior art does not suggest the claimed pH range.

10. Claim 58

The remarks of Section 1 about independent claim 49 also apply to claim 58, and so are not repeated here.

In addition, claim 58 recites that the composition comprises a sugar alcohol at a maximum concentration of 2% (w/v). That limitation is in contradiction to prior art teachings about stable thrombin preparations. For instance, Altshuler points out that the sugar alcohols mannitol, sorbitol, glycerol, and their mixtures should be in a concentration of 10-50% for a thrombin preparation to be stable. (See Altshuler at col. 4, lines 21-39.) When sugar alcohols were in amounts less than 10%, Altshuler explains that the thrombin preparations quickly lost their stability and thrombin activity. (Altshuler at Fig. 3; col. 5, lines 49-63; cols. 6-8, working examples III and VI compared to examples I, II, IV, V, VII, and VIII; and claim 1.) Other documents provide similar teachings. For example U.S. Patent No. 5,397,704, of record, suggests using about 10-40% glycerol by weight, preferably 20-30% by weight, to keep a thrombin preparation stable, while European Application No. 0 221 700 A2, also of record, suggests 25%

glycerol. (*See* 5,397,704, at col. 2, line 61, to col. 3, line 2, and col. 5, lines 50-53; *see* EP 0 221 700 A2 at pages 3-5, Tables I-III.)

Thus, Altshuler and other documents in the general prior art teach away from the invention of claim 58 by suggesting that high concentrations of sugar alcohols are necessary for a thrombin preparation to be stable. In so doing, Altshuler also illustrates that the stability of the preparations of claim 58 is unexpected, as one of ordinary skill at the relevant time period would have expected a thrombin preparation with no sugar alcohol, or a low concentration of sugar alcohol to lose thrombin activity at room temperature relatively rapidly.

For those reasons, as well as the reasons provided in Section 1, claim 58 is not obvious.

11. Claim 59

The remarks of Sections 1 and 10 above also apply to claim 59. Claim 59 includes the limitations of claim 49 and further recites that the sugar, sugar alcohol, amino acid, salt of a mono- or polycarboxylic acid, or salt of a mono- or polyhydroxycarboxylic acid, does not increase the viscosity of the preparation.

As explained in Section 10, such preparations are contrary to the teachings of the prior art. For instance, Altshuler teaches that ingredients known to be viscous, such as sugar alcohols and polyethylene glycol (PEG) must be added to thrombin preparations or they will rapidly lose thrombin activity at room temperatures. (Altshuler at col. 3, lines 3-9; col. 4, lines 21-39; Figure 3; working examples I-VIII at cols. 6-8; and

claims.) Brezniak also conducted thrombin stability studies in a PEG 6000-containing mediuim. (Brezniak at page 847, second column.)

For those reasons, as well as the reasons provided in Section 1, claim 59 is not obvious.

12. Claim 60

The remarks of Section 1 also apply to claim 60, as claim 60 depends from claim 49. In addition, claim 60 recites that the stable thrombin preparation "comprises a hemostatic or a constituent of a hemostatic." In other words, the preparation is part of a pharmaceutical formulation. Given that thrombin as a hemostatic is intended to have the highest possible therapeutic utility, it would have gone against the general understanding of one of ordinary skill in the art at the relevant time to add a thrombin activity inhibitor to such a preparation. Indeed, a noncovalently binding inhibitor of thrombin activity would logically be expected to decrease the therapeutic activity of thrombin. Hence, for that additional reason, claim 60 shows unexpected results and is not obvious.

13. Claim 61

The remarks of Sections 1 and 12 apply also to claim 61, and thus are not repeated here. Thrombin preparations as constituents of tissue glues are part of a pharmaceutical formulation. In such a formulation, addition of a thrombin activity inhibitor would logically be expected to decrease the therapeutic activity of the thrombin preparation, not to maintain it at a high level as claimed here. Hence, claim 61 is also not obvious given the unexpected and fruitful results this invention provides.

In summary therefore, Appellants request the Board to overturn this obviousness rejection with respect to each of claims 49-61.

Conclusion

For the reasons given above, pending claims 49-61 are allowable and Appellants respectfully request the reversal of the Examiner's rejections and the rejoinder of the withdrawn method claims 20-24, 27-30, and 33.

This Appeal Brief is accompanied by a petition for a one-month extension of time and fee payment to extend the reply period to August 9, 2007. To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not found to be enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 9, 2007

By: _____
Elizabeth A. Doherty
Reg. No. 50,894

Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

The following is a list of the currently pending claims and their status.

1.- 19. (Canceled)

20. (Withdrawn) A process for producing the preparation of claim 49, comprising obtaining a prothrombin from plasma or a plasma fraction, activating the prothrombin to thrombin, and purifying the thrombin by hydrophobic interaction chromatography.

21. (Withdrawn) The process as claimed in claim 20, wherein the prothrombin is subjected to inactivation or reduction of viruses during its production.

22. (Withdrawn) The process as claimed in claim 20, wherein the thrombin is subjected to inactivation or reduction of viruses before or after hydrophobic interaction chromatography.

23. (Withdrawn) The process as claimed in claim 20, additionally comprising performing cation exchange chromatography before or after the hydrophobic interaction chromatography.

24. (Withdrawn) The process as claimed in claim 20, wherein the preparation is adjusted to a pH of from 5.0 to 8.0.

25.-26. (Canceled)

27. (Withdrawn) The process as claimed in claim 20, wherein the noncovalently binding inhibitor of thrombin activity is benzamidine or p-aminobenzamidine.

28. (Withdrawn) The process as claimed in claim 20, wherein a gel with coupled hydrophobic radicals is employed as absorbent for the hydrophobic interaction chromatography.

29. (Withdrawn) The process as claimed in claim 28, wherein the hydrophobic radicals.

30. (Withdrawn) The process as claimed in claim 20, additionally comprising filtering the preparation through a membrane with a suitable pore size to remove viruses.

31.-32. (Canceled)

33. (Withdrawn) A method of using the preparation of claim 49, wherein the preparation is administered to a patient in need thereof as a hemostatic, a constituent of a hemostatic or as a constituent of tissue glue.

34.-48. (Canceled)

49. (Previously Presented) A stable thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity as stabilizer, and further comprising at least one soluble calcium salt, sodium chloride as stabilizer, at least one buffer substance, and at least one of

a sugar,

a sugar alcohol,

an amino acid,

a salt of a mono- or polycarboxylic acid, or

a salt of a mono- or polyhydroxycarboxylic acid,

wherein, after at least 12 months of storage at 20-25 °C in the liquid state, the thrombin activity of the preparation, measured by a coagulation test with a fibrinogen substrate, is more than 70% of its initial level prior to the storage.

50. (Previously Presented) The preparation of claim 49, in which the thrombin activity, after at least 12 months of storage at 20-25 °C in the liquid state, is more than 80% of its initial level prior to the storage.

51. (Previously Presented) The preparation of claim 49, in which the thrombin activity, after at least 12 months of storage at 20-25 °C in the liquid state, is more than 90% of its initial level prior to the storage.

52. (Previously Presented) The preparation of claim 49, in which the thrombin activity, after at least 24 months of storage at 20-25 °C in the liquid state, is more than 70% of its initial level prior to the storage.

53. (Previously Presented) The preparation of claim 49, in which the thrombin activity, after at least 24 months of storage at 20-25 °C in the liquid state, is more than 80% of its initial level prior to the storage.

54. (Previously Presented) The preparation of claim 49, in which the thrombin activity, after at least 24 months of storage at 20-25 °C in the liquid state, is more than 90% of its initial level prior to the storage.

55. (Previously Presented) The preparation of claim 49, wherein the noncovalently binding inhibitor of thrombin activity is benzamidine.

56. (Previously Presented) The preparation of claim 49, wherein the noncovalently binding inhibitor of thrombin activity is p-aminobenzamidine.

57. (Previously Presented) The preparation of claim 49, wherein the pH of the preparation is from 5.0 to 8.0.

58. (Previously Presented) The preparation of claim 49, comprising a sugar alcohol at a maximum concentration of 2% (w/v).

59. (Previously Presented) The preparation of claim 49, wherein the at least one of a sugar, a sugar alcohol, an amino acid, a salt of a mono- or polycarboxylic acid, or a salt of a mono- or polyhydroxycarboxylic acid, does not increase the viscosity of the preparation.

60. (Previously Presented) The preparation of claim 49, wherein the preparation comprises a hemostatic or a constituent of a hemostatic.

61. (Previously Presented) The preparation of claim 49, wherein the preparation comprises a constituent of a tissue glue.

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

No evidence pursuant to §§ 1.130-1.132 is submitted herewith.

Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

The present application was the subject of prior Appeal No. 2005-0192.

A copy of that earlier decision is submitted herewith.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte HUBERT METZNER and HEINRICH SCHNEIDER

Appeal No. 2005-0192
Application No. 09/809,021

ON BRIEF

Before SCHEINER, MILLS and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 18, 19, and 35-38. Claims 20-34 are also pending but have been withdrawn from consideration by the examiner. Claim 18 is representative of the subject matter on appeal and reads as follows:

18. A thrombin preparation comprising thrombin and a noncovalently binding inhibitor of thrombin activity as stabilizer, wherein the thrombin preparation is suitable for therapeutic purposes.

The examiner relies on the following references:

Altshuler	4,363,319	Dec. 14, 1982
Hanada et al. (Hanada)	5,945,103	Aug. 31, 1999

Lorne et al. (Lorne), "Transfusion Technology : Purification of Human Thrombin by Affinity Chromatography For Its Use in Biological Glue Preparations," Rev. Fr. Transfus. Hemobiol., Vol. 32, pp. 391- 400 (1989)

Allary et al. (Allary), "Isolation by Affinity Chromatography, on Silica Support, of Human Thrombin for Its Use in Biological Glue Preparations," Annales Pharmaceutiques Francaises, Vol. 48, No. 3, pp. 129-135 (1990)

Brezniak et al. (Brezniak), "High Stability of Dilute Human α-thrombin in Salt [illegible]," Blood Coagulation and Fibrinolysis, Vol. 5, pp. 841-846 (1994)

Claims 18, 35, and 37 stand rejected under 35 U.S.C. § 102(b) as anticipated by either Allary or Lorne.

Claims 18, 19, and 35-38 stand rejected under 35 U.S.C. § 103 as obvious in view of either Allary or Lorne, combined with Hanada, Brezniak, and Altshuler.

We affirm.

Background

"Since it became possible to produce thrombin commercially, several applications thereof have emerged. The main applications . . . are, besides diagnostic [illegible] as a component of a tissue glue together with a fibr[in]ogen-containing component." Specification, paragraph [0002].[1]

"For formulation of the thrombin preparation as a component, which is stable and storable in the liquid and, where appropriate, also in the frozen state, for use in a tissue glue or on its own as a local hemostatic, a buffer should be used to adjust to a pH of

about 5.0 to 8.0. To achieve the desired effect on use and for stabilization, then a soluble calcium salt, sodium chloride, a sugar or a pure alcohol and/or an amino acid . . . is added to the preparation. This results in good stabilities in the liquid and/or frozen state for a storage time of 12 months or more." Paragraph [0016].

"It has also emerged that addition of substances which inhibit noncovalently the thrombin activity in vitro can seemingly only increase the stability even further, especially at room temperature, by diminishing the autolysis of thrombin. Suitable substances for this purpose are compounds such as benzamidine or p-aminobenzamidine." Paragraph [0017].

"The thrombin preparations produced by the described process can be employed inter alia as components of a fibrin glue [in combination with fibrin and optionally factor XIII]." Paragraph [0020]. "Finally, the thrombin concentrates produced according to the invention can also be employed alone or in combination with carrier materials as agent for local stoppage of bleeding." Paragraph [0021].

Discussion

The claims stand or fall together. Appeal Brief, page 5. Since the broadest claim subject to each rejection is claim 18, we will consider that claim as representative. Claims 19 and 35-38 will stand or fall with claim 18.

Claim 18 is directed to a thrombin preparation which is "suitable for therapeutic purposes," comprising thrombin and "a noncovalently binding inhibitor of thrombin

[1] The instant application's official Image File Wrapper contains images of very poor quality; nearly every page is partially illegible. Therefore, our citations to the specification refer to the version of the application that was published on October 25, 2001 as Publication No. 2001/0033837.

activity as stabilizer." The examiner rejected some of the claims as anticipated and all of the claims as obvious in view of the prior art.

1. Anticipation

The examiner rejected claims 18, 35, and 37 as anticipated by either Allary or Lorne, stating the rejection as follows:

> The references each teach that thrombin is eluted off a benzamidine-Sepharose column. Thrombin and benzamidin[e] would be together in the eluate. Since they elute using benzamidine in a competitive elution then a complex of thrombin-benzamidine as in the present claims would have been formed.

Examiner's Answer, page 4.

We agree with the examiner that the experiments described by either Allary or Lorne appear to result in a composition meeting all of the limitations of instant claim 18. Since the references both seem to describe the same experimental procedures, we will limit our discussion to Lorne. Lorne discloses purification of thrombin by affinity chromatography. See pages 5-7.[2] Benzamidine was immobilized on dextran-coated silica beads (Spherodex) and placed inside a column. Page 5. Samples containing thrombin were then injected into the column (id.) and the thrombin was allowed to adsorb onto the immobilized benzamidine (page 6). After the column was washed with buffer to eliminate nonadsorbed proteins, the thrombin was eluted from the column using, in one experiment, a solution comprising 15 mM benzamidine. Page 7, lines 5-6.

[2] Our citations to Lorne refer to the English-language translation, of record. We note that the examiner's statement of the rejection referred only to "Allary et al. (abstract) or Lorne et al. (abstract)." Examiner's Answer, page 4. However, as Appellants noted, the examiner made of record full-text translations of the Allary and Lorne references at the time the Examiner's Answer was mailed. Reply Brief, page 2. We also note that Appellants apparently had access to their own full-text translations prior to writing the Appeal Brief, since partial translations were included in the brief and Appellants offered to provide the full-text

Lorne describes the results of the experiment:

> Benzamidine at the concentration of 15 mmol/l also led to elution of the thrombin. The results are comparable to those obtained with arginine methylester in terms of specific activity (1450 NIH units/mg), yield (approximately 78%), and electrophoretic purity. . . .
>
> Regardless of the elution method selected, the final recovery of this thrombin obtained by chromatography must be done via a preliminary dialysis or ultrafiltration in an NaCl 1 M medium in order to dissociate the complex formed with the elution agent. Next, the salt will be eliminated by dialysis against water and glucose at 10 g/l in order to place the protein in good conditions to lyophilize it.

Page 15.

Thus, the initial eluate described by Lorne (i.e., the eluate prior to the two dialysis treatments described in the last paragraph of the above quote) reasonably appears to be a thrombin preparation comprising enzymatically active thrombin as a complex with benzamidine.

Appellants do not dispute that Lorne's preparation comprises a complex of thrombin and benzamidine, but they argue that the preparation does not anticipate claim 18 because "[r]eview of the full documents shows that . . . neither Lorne nor Allary teaches a preparation comprising both 'thrombin' and a 'noncovalently binding inhibitor of thrombin activity' such that the overall composition with both ingredients is 'suitable for therapeutic purposes.'" Id., page 17. The phrase "suitable for therapeutic purposes," Appellants argue "mean[s] that it can be directly administered to a patient." Id., page 16.

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translations to the Board. See the Appeal Brief, page 17 (footnote 2). Since both Appellants and the examiner apparently considered and relied upon the full-text references, we will do so as well.

Appellants point to the chromatographic procedure used by Allary and Lorne and argue that

> there is no evidence that the eluates from either Lorne or Allary's columns are "suitable for therapeutic purposes" according to claim 18. . . . For example, they may contain unsuitable run-off from the SPHERODEX® columns or unsuitable buffer ingredients. Further, there is no evidence that the thrombin solutions in the chromatography procedure are suitably sterilized.

Id., page 18. Appellants also point to Lorne's disclosure that the thrombin-containing preparation eluted from the column is subjected to two steps of dialysis or ultrafiltration before it is in a form intended for administration to a patient. See id., paragraph bridging pages 17 and 18.

We agree that claim 18 requires the thrombin preparation to be "suitable for therapeutic purposes" and, therefore, the preparations disclosed by Lorne and Allary must meet this limitation in order to anticipate the claim. However, we do not agree that the prior art compositions fail to meet this limitation.

"It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Sneed, 710 F.2d 1544,1548, 218 USPQ 385, 388 (Fed. Cir. 1983) (citation omitted).

In this case, the specification does not define (or even contain) the phrase "suitable for therapeutic purposes." However, the specification describes the claimed thrombin-containing preparation as "use[ful] as local hemostatic or as component of a tissue glue together with a fibr[in]ogen-containing component." Page 1, paragraph

[0002]. Therefore, we will accept, for argument's sake, Appellants' position that the claimed preparation must be in a form that can be directly administered to a patient.

In addition, since the uses disclosed in the specification rely on thrombin's enzymatic activity as part of the blood-clotting process, the claimed preparation must apparently contain enzymatically active thrombin in order to be suitable for therapeutic purposes. We do not, however, interpret the claim to require that the preparation be stable when stored in liquid form, or that it be virus-free, or that it be sterile. While those properties may be desirable for a commercial product, the absence of such properties would not render the preparation therapeutically ineffective. Therefore, they are not required by the phrase "suitable for therapeutic purposes" when that phrase is given its broadest reasonable interpretation in light of the specification.

Based on this interpretation of the claim language, the prior art preparations reasonably appear to be "suitable for therapeutic purposes." Lorne discloses that the thrombin in the eluate had a specific activity of "1450 NIH units/mg"; therefore, the thrombin was enzymatically active. Although Lorne suggests that the thrombin- and benzamidine-containing eluate should be subjected to a two-step dialysis procedure, those dialyses are intended "to place the protein in good conditions to lyophilize it." Page 15. Lorne does not disclose or suggest that the dialyses are required in order to make the thrombin-containing solution therapeutically effective.

In fact, Lorne provides evidence that the standard for therapeutic efficacy is rather low. Lorne teaches that the standard thrombin used in fibrin glues "is of animal origin, specifically equine or bovine." Page 3. Thus, a thrombin-containing preparation

apparently need not even contain human thrombin in order to be "suitable for therapeutic purposes."

We conclude that the compositions disclosed by Lorne and Allary reasonably appear to meet all of the limitations of instant claim 18. The burden therefore shifts to Appellants to provide evidence to the contrary. See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.").

Appellants have provided no evidence to show that the thrombin- and benzamidine-containing eluate disclosed by the prior art is not "suitable for therapeutic purposes." Since the prior art composition reasonably appears to meet all the limitations of instant claim 18, and Appellants have provided no evidence that it does not, we affirm the rejection of claim 18 as anticipated by either Allary or Lorne. Claims 35 and 37 fall with claim 18.

2. Obviousness

The examiner rejected claims 18, 19, and 35-38 as obvious over either Allary or Lorne, combined with Hanada, Brezniak, and Altshuler. As noted above, all of the claims stand or fall together. Therefore, we need only consider claim 18; claims 19 and 35-38 stand or fall with claim 18.

We have already concluded the claim 18 is anticipated by either of Allary or Lorne. Therefore, claim 18 is also obvious in view of either Allary or Lorne, standing

alone. See In re May, 574 F.2d 1082, 1089, 197 USPQ 601, 607 (CCPA 1978) (Anticipation is "the epitome of obviousness.").

Appellants' arguments in response to this rejection are the same as in response to the rejection under 35 U.S.C. § 102, and have been adequately addressed above. The rejection of claim 18 as obvious in view of either Allary or Lorne, combined with Hanada, Brezniak, and Altshuler, is affirmed. Claims 19 and 35-38 fall with claim 18.

Other Issues

Appellants filed an Information Disclosure Statement on September 8, 2003, which does not appear to have been considered by the examiner. On return of this application, the examiner should review the IDS and treat is as appropriate under 37 CFR §§ 1.97 and 1.98.

Summary

The prior art reasonably appears to disclose a composition meeting the limitations of claim 18 and Appellants have provided no evidence to the contrary. We therefore affirm the rejection of claim 18 as both anticipated and obvious. The remaining claims fall with claim 18.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Toni R. Scheiner)
Administrative Patent Judge)
)
)
Demetra J. Mills) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
Eric Grimes)
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